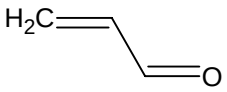
Acrolein Reference Exposure Levels

(2-propenal, acrylic aldehyde, acryladehyde, acraldehyde)

CAS 107-02-8



1. Summary

Acrolein is a powerful irritant. Due to its highly reactive nature, the effects of acrolein are generally limited to the site of contact; skin, eyes and mucous membranes. Inhalation exposure to low levels (≤ 1 ppm) causes irritation of the eyes, nose and throat. Moderately higher exposures may result in severe lacrimation, and irritation of the mucous membranes of the respiratory tract. Death due to respiratory failure has been associated with high level exposures.

1.1 Acrolein Acute REL

Reference Exposure Level	**2.3 μg/m³ (1.0 ppb)**
Critical effect(s)	Subjective ocular irritation
Hazard Index target(s)	Eyes

1.2 Acrolein 8-Hour REL

Reference Exposure Level	**1.6 μg/m³ (0.68 ppb)**
Critical effect(s)	Lesions in respiratory epithelium
Hazard Index target(s)	Respiratory

1.3 Acrolein Chronic REL

Reference Exposure Level	**0.1 μg/m³ (0.05 ppb)**
Critical effect(s)	Lesions in respiratory epithelium
Hazard Index target(s)	Respiratory

2. Physical & Chemical Properties

Description	Colorless or yellow liquid with piercing disagreeable odor
Molecular formula	C_3H_4O
Molecular weight	56.1 g/mol
Density	0.843 g/cm^3 @ 20° C
Boiling point	53° C
Melting point	-87° C
Vapor pressure	220 mm Hg @ 20° C
Flashpoint	-26° C
Explosive limits	2.8% - 31% by volume
Solubility	soluble in ethanol, diethyl ether, and up to 20% w/v in water
Odor threshold	0.5 ppm
Metabolites	glycidaldehyde, acrylic acid
Conversion factor	1 ppm in air = 2.3 mg/m^3 @ 25° C

3. Occurrence and Major Uses

Acrolein is principally used as a chemical intermediate in the production of acrylic acid and its esters. Acrolein is used directly as an aquatic herbicide and algicide in irrigation canals, as a microbiocide in oil wells, liquid hydrocarbon fuels, cooling-water towers and water-treatment ponds, and as a slimicide in the manufacture of paper (IARC, 1995). Combustion of fossil fuels, tobacco smoke, and pyrolyzed animal and vegetable fats contribute to the environmental prevalence of acrolein. Acrolein is a byproduct of fires and is one of several acute toxicants to which firefighters are exposed. It is also formed from atmospheric reactions of 1,3-butadiene. The annual statewide emissions of acrolein from mobile, stationary and natural sources (not including atmospheric transformation) reported in the California Toxics Inventory for 2004 were preliminarily estimated to be 2,242 tons contributing to a statewide ambient level of 0.53 ppb (CARB, 2005b).

4. Metabolism

The metabolism of acrolein comprises several pathways. It rapidly reacts with sulfhydryl groups, especially protein cysteine residues and glutathione. The glutathione conjugate may be oxidized or reduced to mercapturic acids (N-acetyl –S-2-carboxyethylcysteine and N-acetyl-S-3-hydroxypropylcysteine, respectively), with the reduction pathway predominating, followed by urinary elimination. Alternatively, acrolein may be epoxidized to glycidaldehyde, which is in turn attacked by glutathione and oxidatively processed to the mercapturic acid, N-acetyl-S-2-carboxy-2-hydroxyethylcysteine. In a third pathway, the Michael addition of water to acrolein is followed by oxidation to malonic and finally oxalic acids (Parent et al., 1998). The formation of homopolymers of acrolein is thought to occur but appears to be limited to the gut. Acrolein may also be oxidized to acrylic acid, mainly in the liver. Following inhalation exposure, the predominant metabolites are the 3-hydroxypropyl and 2-carboxyethyl mercapturic acids mentioned above (Linhart et al., 1996).

5. Acute Toxicity of Acrolein

5.1 Acute Toxicity to Adult Humans

Sensory irritation is the primary adverse effect associated with acute, low level exposures to acrolein. The irritative effects of acrolein are noticeable at low levels of exposure (≤0.25 ppm) and rapidly become more pronounced with increasing concentration, while brief exposure (1.5 min) to 0.3 ppm (0.7 mg/m³) causes irritation of the eyes and nose (Weber-Tschopp et al., 1977). The powerful irritant and lacrimator properties of acrolein led to its use in gas grenades and artillery shells by the French in 1916. At a concentration of 7 mg/m³, acrolein caused severe lacrimation and irritation of the mucous membranes of the respiratory tract (Prentiss, 1937). A case report of respiratory failure and death in individuals exposed to vapors from overheated frying pans containing fat and food items implicated acrolein as the principal toxicant (Gosselin et al., 1979).

Ocular irritation is one of the most sensitive responses to acrolein. In a study by Darley et al. (1960), 36 human volunteers were exposed to 0.06, 1.3-1.6, and 2.0-2.3 ppm for 5 minutes. Acrolein was dissolved in water and delivered to the eyes in a stream of oxygen through face masks. Carbon-filter respirators were worn during exposure so that only the eyes were exposed to the test material. The subjects, who were without a history of chronic upper respiratory or eye problems, rated the degree of eye irritation every 30 seconds during exposure as none (0), medium (1), or severe (2). The individuals' maximum values were used in the analysis that revealed a concentration-dependent incidence of eye irritation (Table 5.1.1). The lowest observed adverse effect level (LOAEL) for eye irritation in human volunteers was estimated by an unspecified method to be 0.06 ppm (0.14 mg/m³) acrolein during the five minute exposures. A NOAEL was not observed in this study.

Table 5.1.1 Ocular Irritation with Acrolein (from Darley et al., 1960)

Acrolein concentration	Irritation score
Filtered air	0.283
0.06 ppm	0.471
1.3-1.6 ppm	1.182
2.0-2.3 ppm	1.476

Ocular and upper respiratory tract irritation were also examined in a chamber study by Weber-Tschopp et al. (1977) involving healthy volunteers. Thirty one men and 22 women were exposed to increasing acrolein levels (0-0.60 ppm) for 40 min, while 21 men and 25 women were exposed to a constant 0.3 ppm for 60 min. Subjective reports of irritation and annoyance, and objective measures of eye-blink and respiratory rates were taken during the exposure periods. During exposure to increasing levels of acrolein, eye irritation, as measured by subjective report and blink frequency, was a more sensitive measure of irritation than nasal irritation. By comparison, for less reactive volatile compounds in studies surveyed by Doty et al. (2004), the thresholds for ocular and

intranasal irritation were of the same magnitude. In the Weber-Tschopp study of acrolein, significantly ($p<0.01$) higher eye irritation was first observed at 0.07 ppm, and nasal irritation at 0.26 ppm compared to controls. Significant depression of respiratory rates was observed at 0.60 ppm ($p<0.05$). With continuous exposure to 0.3 ppm acrolein, subjective eye and nasal irritation increased rapidly during the first 20 minutes and tended to plateau by 40 min. After 10 min of continuous exposure, a decrease in respiratory rate of 10% was evident in 47% of the subjects, while eye blink rate doubled in 66%. The authors suggest a threshold for adverse effects in the range of 0.09-0.30 ppm.

The effects of irritants such as acrolein may be accentuated in individuals with prior sensitization. Roux et al. (1999) investigated the interaction between passive sensitization of human isolated airways and exposure to pollutants (specifically, ozone and acrolein). Lung tissue from nonatopic, nonasthmatic patients was immunologically sensitized by incubation in sera from atopic asthmatic patients. Roux et al. reported that *in vitro* passive sensitization of the isolated tissues and exposure to acrolein act in a synergistic manner on human bronchial smooth muscle reactivity in response to both specific and nonspecific agonists. In tissues sensitized by incubation in sera from asthmatic patients, preexposure to 0.3 μM acrolein for 10 or 20 minutes significantly increased the maximal contractile response to a specific antigen (*Dermatophagoides pteronyssinus*) by 20.5 ± 6.5 % and 34.9 ± 7.4%, respectively. In addition, in sensitized tissue pre-exposed to 0.3 μM acrolein for 10 minutes, contractile response was increased by 33.5 ± 6.2% and 32.5 ± 5.1% for carbachol and histamine, respectively. Thus acrolein exposure appears to exacerbate asthma.

Mucus hypersecretion is one of the hallmarks of inflammatory airway disorders, including asthma. Borchers et al. (1999b) examined the effect of 0.01-100 nM acrolein on mucus glycoprotein (mucin) gene expression in cultured human airway epithelial cells. After a 4 hour exposure to acrolein in vitro, epithelial cells were found to have elevated mucin mRNA levels. It is not clear whether acrolein acts directly on epithelial cells or indirectly through inflammatory mediators released after acrolein exposure, however, asthma exacerbation is a likely result of acrolein exposure in susceptible individuals.

Predisposing Conditions for Acrolein Toxicity

Medical: Persons with pre-existing eye, skin, respiratory, allergic, asthmatic or heart conditions might be at increased risk due to acrolein exposure. As a respiratory irritant, there is evidence that acrolein exacerbates asthma via the induction of bronchial hyper-responsiveness (Leikauf et al., 1989a; Leikauf et al., 1989b), and mucus hyper-secretion (Borchers et al., 1998; Borchers et al., 1999a; Borchers et al., 1999b). Acrolein has been listed as a TAC that may disproportionately impact children due to concerns related to asthma exacerbation.

Chemical: Cancer patients treated with cyclophosphamide could be at increased risk because acrolein is a metabolite of cyclophosphamide (NTIS, 1981).

5.2 Acute Toxicity to Infants and Children

The literature specifically examining the effects of acrolein inhalation in infants and children is limited and comprises case studies of accidental exposure, and exposures to multiple substances. The most frequent souces of acrolein in childhood exposures are environmental tobacco smoke (ETS) and acrolein formed from overheated cooking oils. Mahut et al. (1993) describe the case of a 27 month-old boy hospitalized for acute respiratory failure following exposure for about an hour to acrid smoke from vegetable oil burning on an electric hot plate. The child was reportedly cyanotic with labored, crackling breathing, and was experiencing severe respiratory acidosis. Eighteen months following exposure, X-ray and CT scans showed bronchial thickening, massive over-inflation, patchy emphysema and diffuse bronchiectasis. In this case, and in cases of exposure to ETS, infants may be more susceptible to the adverse effects of acrolein in part due to an inability to escape exposure. Children also may be more susceptible to the effects of respiratory irritants due to the immature state of their airways.

As noted in OEHHA (2001): "*OEHHA considers asthma to impact children more than adults. Children have higher prevalence rates of asthma than do adults (Mannino et al., 1998). In addition, asthma episodes can be more severe due to the smaller airways of children, and result in more hospitalizations in children, particularly from the ages of 0 to 4 years, than in adults (Mannino et al., 1998; CDHS, 2000)." "Thus, on a population-wide basis, children are more impacted by asthma than adults, and since acrolein exacerbates asthma, children may be more impacted by acrolein toxicity than adults."* Data strongly suggesting that acrolein exacerbates asthma derive from studies using human tissue *in vitro* (Roux et al., 1999; Borchers et al., 1999a) and in animals *in vivo* (Leikauf et al., 1989a; 1989b; Borchers et al., 1998; Borchers et al., 1999b).

5.3 Acute Toxicity to Experimental Animals

Experimental exposures of rodents to acrolein at and above levels that are irritating to the eyes and respiratory tract in humans provide evidence for several adverse effects and their possible mechanisms. Acrolein prompts a proliferative response in nasal epithelium as shown by increased DNA synthesis (Roemer et al., 1993) and expression of mucin genes (Borchers et al., 1998). The latter effect in turn is associated with the hyper-secretion of mucus that may contribute to chronic obstructive pulmonary disease and asthma (Borchers et al., 1998). Bronchial hyper-responsiveness, a hallmark of asthma, increases with acrolein exposure (Leikauf et al., 1989a) supporting a connection between acrolein exposure and exacerbation of asthma in humans. The dose-dependent decreases in protective epithelial enzyme activities (Cassee et al., 1996b) and levels of sulfhydryls (Lam et al., 1985; McNulty et al., 1984) are likely to be involved in the observed formation of lesions in the nasal epithelium (Cassee et al., 1996b).

Table 5.3.1 Acrolein Effects in Experimental Animals

Study	Model	Exposure	Outcome
Roemer et al. 1993	Proliferation of rat nasal and tracheal epithelium	0, 0.2, 0.6 ppm 6 h/d, 1 or 3 d	Increased DNA synthesis at 0.2 ppm (LOAEL)
Borchers et al. 1998	Mucus hyper-secretion, mucin gene expression in rat trachea and lungs	0.3, 0.75, 1.5, 3.0 ppm 6 h/d, 5 d/w	Hyper-secretion and gene expression at 0.75 ppm. (NOAEL = 0.3 ppm)
Leikauf et al. 1989a	Bronchial hyper-responsiveness and airway resistance in guinea pigs	1.3 ppm, 2 h	Resistance increased from 0.86 to 1.29 ml·cm H_2O/ml. Acetylcholine to double airway resistance dropped from 114 to 44.7 μg/kg/min
Buckley et al. 1984	Nasal histopathology at (RD_{50}) in mice;	1.7 ppm, 6 h/d, 5d	Exfoliation and squamous metaplasia of epithelium
Morris et al. 2003	Decrease in respiratory rate (RD_{50}) in mice	0.3, 1.6, 3.9 ppm, 10 min	Control RD_{50} at 1.50 ppm vs 0.82 ppm in allergic mice
Kane et al. 1979	Decrease in respiratory rate (RD_{50}) in mice	15 min	RD_{50} 1.7 ppm
Cassee et al. 1996b	Histopathology of rat nasal epithelium	0, 0.25, 0.67, 1.4 ppm, 6 h/d, 1-3 d	Dose-dependent lesions and decreased enzyme activities in nasal epithelium
Lam et al. 1985	Sulfhydryl depletion in rat respiratory mucosa	0, 0.1, 0.5, 1.0, 2.5 ppm 3 h	Dose-dependent depletion of non-protein sulfhydryls
McNulty et al. 1984	Sulfhydryl depletion in rat respiratory mucosa and liver	0.1, 0.3, 1, 2.5, 5 ppm 3 h	Dose-dependent depletion of non-protein sulfhydryls in nasal mucosa but not liver

Roemer et al. (1993) exposed Male Sprague Dawley rats by inhalation to 0, 0.2 or 0.6 ppm acrolein for 6 h per day on one or three successive days. Nasal and tracheal epithelial and free lung cells were analyzed for proliferative responses using 5-bromodeoxyuridine (BrdU) labeling to identify DNA synthesizing cells. A single exposure to acrolein increased the DNA synthesizing cells 3-fold. After three exposures the increase was distinctly lower. All sites analyzed showed approximately the same concentration/response pattern. Since significant changes in cell proliferation were detected at 0.2 ppm (0.46 mg/m^3) acrolein, it is a LOAEL for this experiment.

Enhanced mucus secretion is a normal airway response to inhaled irritants. However, mucus hypersecretion is involved in the development of chronic obstructive pulmonary diseases; as such, it is considered an adverse effect. Borchers et al. (1998) exposed male rats to 3.0 ppm acrolein for 6 h/d, 5 d/wk for up to 12 days and examined the lungs and trachea for mucin cell metaplasia and expression of the mucin genes MUC2 and MUC5ac. The effects of acrolein concentration on mucin mRNA levels were further examined in rats exposed daily to 0.3, 0.75, 1.5, 3.0 ppm. Acrolein exposure resulted in a time-dependent increase in mucous cell differentiation and mucus hypersecretion in rat lungs. These changes were accompanied by increases in lung MUC5ac mRNA to levels

3-fold higher than in controls, and readily immunohistochemically detectable levels of MUC5ac. MUC5ac mRNA was elevated by concentrations as low as 0.75 ppm while MUC2 mRNA was not affected by any of the levels tested. Thus 0.3 ppm (0.69 mg/m^3) is a NOEL for this effect. The trachea of treated animals showed sloughing of the epithelium accompanied by excessive mucus and inflammatory cells in the lumen.

Bronchial hyper-responsiveness is a hallmark of reactive airway diseases such as asthma, and may be induced by inhaled irritants. Leikauf et al. (1989a) exposed guinea pigs to 1.3 ppm acrolein for 2 h and measured the induction of bronchial hyperresponsiveness by the amount of infused acetylcholine necessary to double specific airway resistance 1, 2, 6, and 24 h after exposure compared to baseline. The dose of acetylcholine required to double airway resistance decreased from 114.0 ± 6.6 to 44.7 ± 4.2 μg/kg/min ($p < 0.001$) at 2 h following acrolein exposure and remained low for at least 24 h. Acrolein exposure was found to increase levels of the bronchoconstrictor leukotriene C_4 (LTC_4) in bronchoaveolar lavage fluids prior to the observation of bronchial hyperresponsiveness. This hyperresponsiveness was prevented by treatment with an inhibitor of LTC_4 synthesis or an LTC_4 receptor antagonist. Acrolein was thus shown to induce bronchial hyperresponsiveness, an effect apparently mediated by LTC_4.

Buckley et al. (1984) investigated whether lesions occur in the respiratory tract of Swiss-Webster mice after exposure to the RD_{50} concentrations of ten sensory irritants including acrolein. After exposure of mice for 6 hr/day for 5 days to 1.7 ppm acrolein, the respiratory tract was examined for histopathologic changes. Acrolein (and all other irritants) produced lesions in the nasal cavity with a distinct anterior-posterior severity gradient. Acrolein specifically caused severe exfoliation and squamous metaplasia of the respiratory epithelium and moderate ulceration of the olfactory epithelium. Acrolein did not induce lesions in the lower respiratory tract.

Morris et al. (2003) compared the respiratory responses to acrolein in healthy mice with those in mice previously sensitized to ovalbumin. Inhalation exposure to ovalbumin prior to acrolein exposure elicited an allergic response in the sensitized mice that was characteristic of allergic airway disease. Upon subsequent acrolein exposure, the RD_{50}, a measure of the dose required to reduce the respiratory rate by 50%, was 1.50 ppm in naïve mice and 0.82 ppm in the mouse model of allergic airway disease. Thus in sensitized animals, a lower concentration of acrolein is required to elicit the same changes in breathing rate observed in non-allergic animals. In both intact mice and in isolated mouse upper respiratory tracts, acrolein exposure caused a significant ($P < 0.05$) increase in flow resistance, an effect that was immediate and not exposure time dependent. Pretreatment with capsaicin to defunctionalize sensory neurons significantly attenuated the breathing rate and obstructive responses supporting the role of sensory neuron stimulation in the response to acrolein. For comparison, Kane et al. (1979) also used the RD_{50} as a measure of sensory irritation and estimated an RD_{50} of 1.7 ppm in mice during 15 minutes of acrolein exposure.

Cassee et al. (1996b) exposed male Wistar rats to 0, 0.25, 0.67, or 1.4 ppm acrolein for 6 h per day on one or three successive days. Immediately following the last exposure, the

rats were killed. Mucosa from the respiratory or olfactory parts of the nose were collected from 3 rats per group for biochemical analyses. The skulls of the other rats in each group were prepared for histopathology and cell proliferation measurements. Nasal epithelium, examined microscopically, showed dose-dependent evidence of disarrangement, necrosis, thickening, and desquamation of the respiratory/transitional epithelium (Table 5.3.2). Significant basal cell hyperplasia, observed at the lowest dose (0.25 ppm), increased with exposure. The activity of glutathione reductase (GR) was reduced after one-day exposure to acrolein, while the activities of GR, glutathione-S-transferase and aldehyde dehydrogenase were reduced following the three-day exposures. These results and those mentioned below suggest that acrolein interferes with enzyme systems involved in its detoxification.

Table 5.3.2 Nasal Lesions in Rats with Acrolein Exposure
(from Cassee et al., 1996b)

Site and type of lesion	Extent	Incidence	
		Low	Medium
Noses examined		5	6
Disarrangement, necrosis, desquamation of respiratory, transitional epithelium	Slight (mainly disarrangement)	4	3
	Moderate	1	3
	Severe and extensive	0	0
Basel cell hyperplasia and/or increased mitotic figures	Slight (focal)	3	2
	Moderate	0	4
	Severe (extensive)	0	0

Pronounced and possibly irreversible biochemical changes occur with acrolein levels that are extremely irritating. Acrolein depletes glutathione (GSH) and other free thiol groups both in vitro and in vivo (McNulty et al., 1984; Lam et al., 1985; Grafstrom et al., 1987; U.S.EPA, 2003; Yang et al., 2004). Inhalation exposure of rats to a concentration of 5 ppm (11.4 mg/m³) for 3 hours caused irreversible depletion of non-protein sulfhydryls in the nasal mucosa (Lam et al., 1985). Under similar exposure conditions, 5 ppm (11.5 mg/m³) for 3 hours, McNulty et al. (1984) reported a 63% decrease in glutathione in nasal mucosal but not in liver. In addition, ^{14}C-labeled acrolein has been shown to bind irreversibly to sulfhydryl groups on cytochrome P450 in rats (Gurtoo et al., 1981). The binding of acrolein to sulfhydryl groups is localized to the area of contact (e.g., nasal membranes or lung epithelium), and is not a systemic effect (Lam et al., 1985).

The pulmonary immunological defense against a bacterial challenge using *Staphylococcus aureus* in mice was impaired in a dose-dependent manner following a single exposure to acrolein at concentrations of 3 and 6 ppm (6.9 and 13.8 mg/m^3) for 8 hours (Astry and Jakab, 1983). In this study, the control exposure was not described.

6. Chronic Toxicity of Acrolein

6.1 Chronic Toxicity to Adult Humans

Information regarding the chronic toxicity of acrolein in humans is limited. There is inadequate direct evidence for carcinogenicity of acrolein in humans or experimental animals (IARC, 1985). However, a metabolite of acrolein, the reactive epoxide glycidaldehyde, has been shown to be mutagenic and carcinogenic in mice and rats. Therefore, acrolein has been designated a Group C substance, with possible human carcinogenic potential (U.S.EPA, 1987). In addition, acrolein-DNA adducts have been found in aortic tissue following 6 hr inhalation exposure to 1 and 10 ppm acrolein (Penn et al., 2001).

A source of chronic acrolein exposure for some individuals is tobacco smoking. Much of the pulmonary irritancy associated with tobacco smoke has been attributed to acrolein and research in this area suggests mechanisms for some of acrolein's pulmonary effects. As part of a defense response, pulmonary neutrophils release oxidants, proteases and cytokines such as IL-8, all of which may promote inflammation and potentiate tissue damage. To limit tissue damage and resolve the inflammation, neutrophils normally undergo consitutive apoptosis. Experiments with isolated human neutrophils exposed to acrolein at levels achievable during active smoking (1-50 μM) found that acrolein inhibited neutrophil apoptosis, increased IL-8 production, and activated mitogen-activated protein kinases (MAPK) (Finkelstein et al., 2001). At acrolein concentrations up to 10 μM, inhibition of apoptosis was accompanied by increased cell viability. At higher acrolein levels, cell viability decreased as necrotic cell death increased. While the mechanisms behind acrolein's concentration-dependent effects on neutrophils are not clear, the effects observed at the lower exposure levels suggest that acrolein may contribute to pulmonary inflammation and exacerbate allergic responses by prolonging the survival of neutrophils, and stimulating the production of inflammation-related cytokines and enzymes. At higher levels, frank cellular toxicity becomes more prominent.

6.2 Chronic Toxicity to Infants and Children

No data addressing the effects of chronic acrolein exposure among infants and children were located. Inasmuch as acrolein is one of the major irritants in environmental tobacco smoke (Takabe et al.) at relatively high concentrations in smokers' homes (1.6-3.6 $\mu g/m^3$; 0.70-1.57 ppm (Nazaroff and Singer, 2004)), children living with smokers may be disproportionately exposed to acrolein as they are less able to avoid exposure than are adult nonsmokers. To the extent that respiratory irritants such as acrolein elicit bronchoconstriction and excessive mucus secretion characteristic of asthma, children, with their smaller airways and greater prevalence of asthma, may experience more diminution of pulmonary function and more episodes of asthma with chronic exposure.

6.3 Chronic Toxicity to Experimental Animals

Long-term exposure to acrolein causes structural and functional changes in the respiratory tract. These effects were examined in male Fischer-344 rats exposed for 6 hours/day, 5 days/week for 62 days to acrolein at concentrations of 0, 0.4, 1.4, and 4.0 ppm (0, 0.92, 3.2, and 9.2 mg/m^3)(Kutzman, 1981; Kutzman et al., 1985). Each group of 24 animals was assessed for pulmonary function immediately prior to the end of the experiment. Pulmonary function tests included lung volumes, forced respiratory capacity, pulmonary resistance, dynamic compliance, diffusing capacity of carbon monoxide, and multi-breath nitrogen washout. At the end of the experiment, animals were killed and histopathological changes in the lungs were recorded. Eight additional rats were designated for histopathology and 8 rats were used for reproductive testing only. All analyses were performed at 6 days post-exposure to minimize the acute effects of acrolein. Mortality was high (56%) in rats exposed to 4.0 ppm (9.2 mg/m^3). The observed mortality was due to acute bronchopneumonia in these cases. The animals from this group that survived had reduced body weight. No histological changes were observed in extra-respiratory tissues in any group. There was a concentration-dependent increase in histological changes to the nasal turbinates (increased submucosal lymphoid aggregates), beginning at 0.4 ppm. Concentration-dependent damage to the peribronchiolar and bronchiolar regions included epithelial necrosis and sloughed cells lying free in the lumen. No lung lesions were observed in the 0.4 ppm group. The LOAEL for nasal lesions (squamous epithelial metaplasia and neutrophil infiltration) in this study was 0.4 ppm.

Feron et al. (1978) exposed groups of 20 Syrian golden hamsters, 12 SPF Wistar rats and 4 Dutch rabbits (of both sexes) to acrolein vapor at 0, 0.4, 1.4 and 4.9 ppm (0, 0.92, 3.2, and 11.3 mg/m^3) 6 h/d, 5 d/wk for 13 weeks. The most prominent effects at the highest level included mortality in rats (3 of each sex), and ocular and nasal irritation, growth depression, and histopathological changes of the respiratory tract in each species. The changes in the airways induced by acrolein consisted of destruction, and hyperplasia and metaplasia of the lining epithelium accompanied by inflammatory alterations. Rats were the most susceptible species examined and showed treatment-related histopathological abnormalities in the nasal cavity down to 0.4 ppm (LOAEL), whereas this level was a NOAEL in hamsters and rabbits. The results for individual rats at 0.4 ppm were not given.

Bouley et al. (1975; 1976) exposed male SPF OFA rats continuously to 0.55 ppm (1.3 mg/m^3) of acrolein for up to 63 days. This level of acrolein led to a greater susceptibility to airborne *Salmonella enteritidis* infection during the first three weeks compared to control rats but it disappeared spontaneously when exposure was continued beyond three weeks. The general toxic effect of diminished weight gain (due to reduced feeding) compared to the control group lasted as long as exposure and disappeared only after acrolein was discontinued. Sneezing, a sign of nasal irritation, was consistently observed in the exposed animals on days 7 through 21 but ceased thereafter. No histopathology of the nasal cavity of or any other tissue was reported.

In one of the few chronic studies reported, Feron and Kruysse (1977) exposed hamsters (18/gender) to 4 ppm (9.2 mg/m^3) acrolein for 7 hours/day, 5 days/week, for 52 weeks. Mild to moderate histological changes were observed in the upper and lower respiratory tract. No evidence of toxicity to other organs was apparent at necropsy, although body weight was decreased. Hematology, urinalysis, and serum enzymes were not affected by exposure. Thus 4 ppm is a chronic LOAEL for hamsters. As noted above, hamsters appear to be a less sensitive species than rats (Feron et al., 1978).

Exposures of rodents have generally formed the basis for the determination of acrolein's chronic effects. However, an interspecies comparison was conducted by Lyon and associates (Lyon et al., 1970) who investigated the effects of repeated or continuous exposures of acrolein on Sprague-Dawley rats (n = 15/exposure group), guinea pigs (n = 15), beagle dogs (n = 2), and male squirrel monkeys (n = 9). Animals were exposed to 0.7 or 3.7 ppm (1.6 or 8.5 mg/m^3) acrolein for 8 hours/day, 5 days/week, for 6 weeks, or continuously to 0.22, 1.0, or 1.8 ppm (0.5, 2.3, or 4.1 mg/m^3) for 90 days. The results below suggest that dogs and monkeys were more susceptible to acrolein's effects than were the rodents.

Two monkeys in the 3.7 ppm intermittent exposure group died within 9 days. Monkeys and dogs salivated excessively during the first week. Squamous metaplasia and basal cell hyperplasia of the trachea were observed in monkeys and dogs; 7 of the 9 monkeys repeatedly exposed to 3.7 ppm also exhibited bronchiolitis obliterans with squamous metaplasia in the lungs. Bronchopneumonia was noted in the dogs. Inflammation in the lung interstitiae was more prominent in the dogs than in the monkeys. Rats and guinea pigs did not exhibit signs of toxicity when exposed intermittently to 3.7 ppm. Continuous exposure to 1.0 and 1.8 ppm, but not 0.22 ppm acrolein, resulted in salivation and ocular discharge in the monkeys and dogs. Rats and guinea pigs appeared normal at all concentrations. Rats exhibited significant weight loss in the 1.0 and 1.8 ppm continuous exposure groups. Nonspecific inflammatory changes were observed in sections of brain, heart, lung, liver and kidney from all species exposed to 1.8 ppm. The lungs from the dogs showed confluent bronchiopneumonia. Focal histological changes in the bronchiolar region and the spleen were detected at 0.22 ppm in dogs. Nonspecific inflammatory changes at the 0.22 ppm level were apparent in liver, lung, kidney and heart from monkeys, guinea pigs and dogs. Unfortunately the nasal cavity was not examined in this study. While there were no unexposed control animals for any species, the cross-species comparison shows substantial interspecies variability in susceptibility.

7. Developmental and Reproductive Toxicity

There are no reports of reproductive or developmental toxicity following inhalation exposure to acrolein. Kutzman (1981) studied reproductive fitness in male and female rats following acrolen inhalation for 6 h/d, 5 d/wk for 62 days. Treated males were mated with untreated females, and treated females with untreated males. No treatment-related differences were found in the parameters assessed including pregnancy rate, number of corpora lutea, embryo viability, early and late deaths, and preimplantation losses.

Similarly, the morphology of sperm collected from the epididymides of treated males was examined and reportedly not affected. Bouley et al. (1975; 1976) exposed three male and 21 female SPF-OFA rats continuously to 0.55 ppm (1.26 mg/m^3) acrolein vapor for 25 days. The rats were allowed to mate on day 4 of the exposure. The number of acrolein-exposed pregnant rats and the number and mean body weight of their fetuses were similar to controls.

In rats, acrolein can induce teratogenic and embryotoxic effects when administered directly into the amniotic fluid, or when added to cultured rat embryos (Slott and Hales, 1986). Additionally, acrolein injected into chicken embryos resulted in embryotoxicity and some teratogenic effects at moderate to high doses (0.001-0.1 mg/egg) (Chhibber and Gilani, 1986). However, intravenous injection of acrolein in pregnant rabbits showed no developmental effects in the offspring (Claussen et al., 1980). Based on this latter study, the World Health Organization (1992) concluded that human exposure to acrolein was unlikely to affect the developing embryo.

8. Derivation of Reference Exposure Levels

8.1 Acrolein Acute Reference Exposure Level

Study	Darley et al., 1960
Study population	36 healthy human volunteers
Exposure method	5 min exposure: carbon-filter respirators worn
Exposure continuity	
Exposure duration	5 min
Critical effects	subjective ocular irritation
LOAEL	0.06 ppm
NOAEL	not observed
Benchmark concentration	not derived
Time-adjusted exposure	not applied
Human Equivalent Concentration	n/a
LOAEL uncertainty factor (UF_L)	6 (default: mild effect, no NOAEL)
Subchronic uncertainty factor (UFs)	not applied
Interspecies uncertainty factor	
Toxicokinetic (UF_{A-k})	1 (default: human study)
Toxicodynamic (UF_{A-d})	1 (default: human study)
Intraspecies uncertainty factor	
Toxicokinetic (UF_{H-k})	1 (site of contact; no systemic effects)
Toxicodynamic (UF_{H-d})	10 (greater susceptibility of children to asthma exacerbation)
Cumulative uncertainty factor	60
Reference Exposure Level	**2.3 μg/m³ (1.0 ppb)**

Acute Reference Exposure Levels are levels at which intermittent one-hour exposures are not expected to result in adverse health effects (see Section 5 of the Technical Support Document).

The study by Darley et al. (1960) was selected as the best available acute exposure study employing human subjects. In addition, the ocular mucosa and the nasal mucosa are both innervated by cranial nerve V (trigeminal nerve). As noted by Doty et al. (2004), numerous studies employing n-alcohols, ketones, alkylbenzenes, terpenes, butyl acetate and toluene, report thresholds for ocular and intranasal irritation to be of the same magnitude suggesting that for most volatiles, tests of ocular and nasal irritancy are of equivalent sensitivity. Thus the endpoint of ocular irritancy used in this study is expected to also reflect irritancy of the upper respiratory tract. Confidence in this REL calculation is moderate as the LOAEL used is based on an estimated LOAEL of 0.06 ppm rather than a measured level. A default uncertainty factor of 6 is associated with the use of a LOAEL for mild effects in the absence of a NOAEL (see Section 4.4.5 of the TSD). Due to its high reactivity, the effects of exposure to acrolein in the air are largely confined to the site of contact, in this case the eyes, with negligible or no systemic effects. This localization of effects to the site of contact is supported by the confinement of acrolein's effects to the upper respiratory tract in the animal studies of acute inhalation exposure. Based on modeling of adults and 3-month old children that takes into account age-related ventilation rates and respiratory tract surface area, the deposition kinetics of reactive gases are generally thought not to be greatly different between adults and children (Ginsberg et al., 2005). Because of this, a value of 1 is used for the kinetic component of the intraspecies uncertainty factor (UF_{H-k}), rather than a more extended values of √10 or 10 which are used where metabolic processes also contribute to inter-individual variability. While ocular irritation is not expected to be substantially different between children and adults, the respiratory irritant effect, with documented potential to exacerbate asthma, is clearly an effect with the potential to differentially impact infants and children. The toxicodynamic component of the intraspecies uncertainty factor UF_{H-d} is therefore assigned an increased value of 10 to account for potential asthma exacerbation. These considerations are applied equally to the acute, 8-hour and chronic REL. The acute REL for acrolein exposure is calculated to be 2.3 $\mu g/m^3$ (1.0 ppb).

The acute REL above is supported by a study in humans by Weber-Tschopp et al. (1977). During a 40 min exposure to increasing concentrations of acrolein, significant ocular irritation was first reported at 0.07 ppm. This represents the LOAEL for this effect and is similar to the LOAEL of 0.06 ppm in Darley et al. (1960). The same uncertainty and adjustment factors, and rationale apply as in Darley, giving an acute REL of 2.7 $\mu g/m^3$ (1.2 ppb).

Study	Weber-Tschopp et al. (1977)
Study population	54 healthy human volunteers
Exposure method	Exposure chamber
Exposure continuity	Increasing concentration (0-0.6 ppm)
Exposure duration	40 min
Critical effects	subjective ocular irritation
LOAEL	0.07 ppm
NOAEL	not observed
Benchmark concentration	not derived
Time-adjusted exposure	not applied
Human Equivalent Concentration	n/a
LOAEL uncertainty factor (UF_L)	6 (default: mild effect, no NOAEL)
Subchronic uncertainty factor (UFs)	not applied
Interspecies uncertainty factor	
Toxicokinetic (UF_{A-k})	1 (default: human study)
Toxicodynamic (UF_{A-d})	1 (default: human study)
Intraspecies uncertainty factor	
Toxicokinetic (UF_{H-k})	1 (site of contact; no systemic effects)
Toxicodynamic (UF_{H-d})	10 (asthma exacerbation in children)
Cumulative uncertainty factor	60
Reference Exposure Level	**2.7 μg/m³ (1.2 ppb)**

A similar acute REL was calculated as shown below based on lesions in nasal epithelium in rats exposed to acrolein for 6 h/d for 3 d (Cassee et al., 1996b). There were sufficient data in this study to permit the application of the BMD method in preference to the NOAEL/LOAEL approach. A $BMC_{0.5}$ of 56 μg/m^3 was derived based on the incidence of moderate to severe lesions at each exposure level. Irritancy was not the endpoint in this study so a time adjustment was applied using $C^n*T=K$ (n=3) to adjust the 18 hours of exposure to 1 hour that gave 147 μg/m^3 (see Section 5.7.1 of the TSD). Interspecies uncertainty factors of 2 for toxicokinetic differences with use of a dosimetric adjustment factor (DAF) of 0.85 (dosimetric adjustment factor – described below and in Section 4.4.7.2.2 of the TSD), and √10 for toxicodynamic variability were combined with a combined intraspecies UF of 10 (1 for kinetic and 10 for dynamic variability, reflecting the expectation of greater toxicodynamic variability) for a cumulative UF of 60 and an acute REL of 0.91 ppb.

Study	Cassee et al., 1996b
Study population	11 rats
Exposure method	
Exposure continuity	6 hr/day
Exposure duration	3 days
Critical effects	lesions of the respiratory epithelium
LOAEL	1.73 ppm
NOAEL	not observed
Benchmark concentration (BMC_{05})	56 µg/m^3
Time-adjusted exposure	C^n*T n = 3
Extrapolated concentration	147 µg/m^3 $(56^3*6/1*3/1)^{1/3}$
Human concentration adjustment	125 µg/m^3 = 147*0.85 (DAF)
LOAEL uncertainty factor (UF_L)	not applied
Subchronic uncertainty factor (UFs)	not applied
Interspecies uncertainty factor	
Toxicokinetic (UF_{A-k})	2 (with DAF adjustment)
Toxicodynamic (UF_{A-d})	√10 (default: no interspecies toxicodynamic data)
Intraspecies uncertainty factor	
Toxicokinetic (UF_{H-k})	1
Toxicodynamic (UF_{H-d})	10 (asthma exacerbation in children)
Cumulative uncertainty factor	60
Reference Exposure Level	**2.1 µg/m^3 (0.91 ppb)**

The DAF is a factor derived by OEHHA based on the modeled comparative flux of formaldehyde in the upper respiratory tracts of rats, rhesus monkeys and humans by Kimbell et al. (2001) (see Section 4.4.7.2.2 of the TSD). Kimbel et al used three-dimensional, anatomically realistic, computational flow dynamic models to estimate mass flux across 20 consecutive bins representing the nasal passages. The mean flux at each bin was weighted by the percent of non-squamous epithelium in that bin to derive a weighted average flux for each bin. Averaging across all 20 bins provides an overall estimate of the flux for comparison between species (rat 13.63 pmol/mm^2; human 30.80 pmol/mm^2). Peak flux values were also estimated for the rat (2620 pmol/mm^2) and human (2082 pmol/mm^2), and averaged with the mean flux values to estimate the DAF (0.85). The DAF is the ratio of this value for the rat to that for humans. Although acrolein is more reactive than formaldehyde, both compounds appear to have their effects primarily on the respiratory (vs. olfactory) epithelium (Cassee et al., 1996a). This supports the assumption that in applying the DAF to acrolein, acrolein and formaldehyde deposit similarly in the nasal passages. In the absence of acrolein-specific modeling data, any residual uncertainty associated with this assumption is reflected in the use of an interspecies UF_{A-k} of 2.

8.2 Acrolein 8-Hour Reference Exposure Level

Study	Kutzman et al., 1985
Study population	96 adult Fisher-344 rats
Exposure method	Discontinuous whole body 0.4 – 4.0 ppm
Exposure continuity	6 hr/day, 5 days/week
Exposure duration	62 days
Critical effects	Lesions in the respiratory epithelium
LOAEL	0.4 ppm
NOAEL	not observed
Benchmark concentration	not derived
Time-adjusted exposure	$C^n * T = K$, where n =1.2
Extrapolated 8 hour concentration	310 ppb = $(0.4^{1.2}*6/8)^{1/1.2}$
Human concentration adjustment	260 ppb = 310*0.85 (DAF)
LOAEL uncertainty factor (UF_L)	6 (default: mild effect, no NOAEL)
Subchronic uncertainty factor (UFs)	not applied
Interspecies uncertainty factor	
Toxicokinetic (UF_{A-k})	2 (default with DAF adjustment)
Toxicodynamic (UF_{A-d})	√10 (default: no interspecies toxicodynamic data)
Intraspecies uncertainty factor	
Toxicokinetic (UF_{H-k})	1
Toxicodynamic (UF_{H-d})	10 (asthma exacerbation in children)
Cumulative uncertainty factor	380
Reference Exposure Level	**1.6 μg/m³ (0.68ppb)**

The 8-hour Reference Exposure Level is a concentration at or below which adverse non-cancer health effects would not be anticipated for repeated 8-hour exposures (see Section 6 in the TSD).

The 8-hour and chronic RELs are based on the observation of lesions in rat respiratory epithelium by Kutzman et al. (1985) following exposure to acrolein for 6 h/d, 5 d/wk for 62 d. The critical effect of lesion formation is not a sensory irritancy effect so a time (T) adjustment was applied using $C^n * T = K$, where n =1.2 (Table G-1, Appendix G of the TSD) to extrapolate to an 8 hour concentration of 310 ppb. Use of C^n (where C is concentration) is a modification of Haber's Law as described in Section 5.7.1 of the TSD. K is a constant. A UF of 6 was applied for the use of a LOAEL. An adjusted human concentration of 260 ppb was estimated using a DAF of 0.85 (see previous section for a discussion of the DAF). Use of the DAF is expected to correct for pharmacokinetic differences between species so an interspecies kinetic UF of 2 was used instead of √10. The default interspecies UF_{A-d} of √10 was applied to compensate for the absence of data on pharmacodynamic differences between species. An intraspecies UF_{H-k} of 1 was used since, although the data are only for adult animals, the pharmacokinetic differences between adult and young animals are not expected to be great based on the similar inhalation dosimetry associated with reactive gases in adults and infants (Ginsberg et al., 2005). The potential pharmacodynamic differences among individuals (especially those

with and without asthma) and between adults and infants (due to the immaturity of the infants respiratory tract) are expected to be greater. For example, irritant gases more readily stimulate the hyper-reactive airways of asthmatics while enhanced mucus production in response to irritant gases may more easily block the infant's narrower airways. As described in Section 5.2, exacerbation of asthma by acrolein is expected to disproportionately affect children. For these reasons, an intraspecies UF_{H-d} of 10 was employed. The UF_{H-d} of 10 is the default in the absence of human kinetic data. This resulted in a cumulative UF of 380 and an 8-hour REL of 1.6 μg/m³ (0.68 ppb).

8.3 Acrolein Chronic Reference Exposure Level

Study	Kutzman et al., 1985
Study population	96 adult Fischer-344 rats
Exposure method	Discontinuous whole body to 0 – 4.0 ppm
Exposure continuity	6 hr/day, 5 days/week
Exposure duration	62 days
Critical effects	Lesions in the respiratory epithelium
LOAEL	0.4 ppm
NOAEL	not observed
Benchmark concentration	not derived
Time adjusted exposure	0.071 ppm = 0.4*6/24*5/7
Human concentration adjustment	60 ppb = 0.071 * 0.85 (DAF)
LOAEL uncertainty factor (UF_L)	6 (default: mild effect, no NOAEL)
Subchronic uncertainty factor (UFs)	√10 (exposure 8-12% of lifetime)
Interspecies uncertainty factor	
Toxicokinetic (UF_{A-k})	2 (with DAF adjustment)
Toxicodynamic (UF_{A-d})	√10 (default: no interspecies toxicodynamic data)
Intraspecies uncertainty factor	
Toxicokinetic (UF_{H-k})	1
Toxicodynamic (UF_{H-d})	10 (asthma exacerbation in children)
Cumulative uncertainty factor	1200
Reference Exposure Level	**0.12 μg/m³ (0.05 ppb)**

The chronic Reference Exposure Level is a concentration at which adverse noncancer health effects would not be expected from chronic exposures (see Section 7 in the Technical Support Document).

The chronic REL was developed based on the same study as the 8-hr REL but with a time extrapolation to continuous exposure since the endpoint was not trigeminal irritancy (see Section 1.2.3 in the TSD). In addition to the UFs applied to the 8-hr REL, a UF of √10 was applied since this was a subchronic exposure study representing 8-12% of the rat's lifetime. The cumulative UF of 1200 gives a chronic REL of 0.12 μg/m³ (0.05 ppb). For comparison with the proposed chronic REL, a chronic REL was estimated from the data of Feron et al. (1978) in rats, which found a LOAEL of 0.4 ppm after exposure for 13 weeks. Using time extrapolation and a DAF of 0.85, a human equivalent

concentration of 60 ppb (138 μg/m^3) was calculated. A UF of 6 was applied for LOAEL to NOAEL conversion, √10 for use of subchronic exposure, and √10 for interspecies toxicodynamic variability. A factor of 2 was used for interspecies toxicokinetic uncertainty associated with the use of the DAF. For intraspecies variability, while these data are from adult animals, a UF_{H-k} of 1 was used since the pharmacokinetic differences between adult and young animals are not expected to be as great as the potential pharmacodynamic differences, for which an intraspecies UF_{H-d} of 10 was employed. This gave an estimated chronic REL of 0.12 μg/m^3 (0.05 ppb). This study was considered supportive of the Kutzman results.

Study	Feron et al. (1978)
Study population	48 adult Wistar rats
Exposure method	Discontinuous whole body to 0 – 4.9 ppm
Exposure continuity	6 hr/day, 5 day/week
Exposure duration	13 weeks
Critical effects	Lesions in respiratory epithelium
LOAEL	0.4 ppm
NOAEL	not observed
Benchmark concentration	not derived
Time-adjusted exposure	0.071 ppm = 0.4*6/24*5/7
Human concentration adjustment	60 ppb = 0.071 * 0.85 (DAF)
LOAEL uncertainty factor (UF_L)	6 (default: mild effect, no NOAEL)
Subchronic uncertainty factor (UFs)	√10 (exposure 8-12% of lifetime)
Interspecies Uncertainty Factor	
Toxicokinetic (UF_{A-k})	2 (with DAF adjustment)
Toxicodynamic (UF_{A-d})	√10 (default: no interspecies toxicodynamic data)
Intraspecies Uncertainty Factor	
Toxicokinetic (UF_{H-k})	1
Toxicodynamic (UF_{H-d})	10 (asthma exacerbation in children)
Cumulative uncertainty factor	1200
Reference Exposure Level	**0.12 μg/m^3 (0.05 ppb)**

The U.S. EPA (2003) based its RfC of 0.02 μg/m^3 on the study by Feron et al. (1978) from which a HEC of 0.02 mg/m^3 was derived based on a regional gas dosimetric ratio (RGDR) of 0.14 and an adjusted LOAEL of 0.16 mg/m^3 (0.14 * 0.16 = 0.02). U.S. EPA applied a total uncertainty factor of 1,000 (3 for interspecies extrapolation from a dosimetrically adjusted dose; 10 for intra-human variability; 3 for the use of a LOAEL; 10 for subchronic to chronic extrapolation). In contrast to the RGDR of 0.14, to better account for differences in rat and human exposures to reactive gases, OEHHA used a DAF of 0.85 based on comparative modeling of gas flux in human and rat nasal passages described above instead of a RGDR. This, combined with UFs of 6 for interspecies uncertainty (2 for use of the DAF, √10 for toxicodynamic differences), √10 for the use of a subchronic study, and 6 for the use of a LOAEL (vs US EPA's 3, 3, and 10, respectively) account for the difference between the REL and the U.S. EPA RfC.

For comparison, the state of Minnesota Department of Health reports a subchronic Health Risk Value (HRV) for acrolein of 0.2 $\mu g/m^3$, a level thought to be without significant risk following inhalation exposure for 13 weeks (MDH, 2002).

8.4 Acrolein as a Toxic Air Contaminant

Acrolein was designated by the ARB as a toxic air contaminant (TAC) in accordance with section 39657(b) of the California Health and Safety Code on April 8, 1993 (Title 17, California Code of Regulations, section 93001)(CCR, 2007). In view of the differential impacts on infants and children identified in Section 6.2 (more severe effects associated with bronchoconstriction and asthma exacerbation, less ability to escape or avoid exposure), OEHHA identified acrolein as a TAC which may disproportionately impact children pursuant to Health and Safety Code, Section 39669.5(c).

9. References

Astry CL and Jakab GJ (1983). The effects of acrolein exposure on pulmonary antibacterial defenses. Toxicol Appl Pharmacol 67(1): 49-54.

Borchers MT, Carty MP and Leikauf GD (1999a). Regulation of human airway mucins by acrolein and inflammatory mediators. Am J Physiol 276(4 Pt 1): L549-55.

Borchers MT, Wert SE and Leikauf GD (1998). Acrolein-induced MUC5ac expression in rat airways. Am J Physiol 274(4 Pt 1): L573-81.

Borchers MT, Wesselkamper S, Wert SE, Shapiro SD and Leikauf GD (1999b). Monocyte inflammation augments acrolein-induced Muc5ac expression in mouse lung. Am J Physiol 277(3 Pt 1): L489-97.

Bouley G, Dubreuil A, Godin J, Boisset M and Boudene C (1976). Phenomena of adaptation in rats continuously exposed to low concentrations of acrolein. Ann Occup Hyg 19(1): 27-32.

Bouley G, Dubreuil A, Godin J and Boudene C (1975). [Effects in the rat of a weak dose of acrolein inhaled continuously]. Eur J Toxicol Environ Hyg 8(5): 291-7.

Buckley LA, Jiang XZ, James RA, Morgan KT and Barrow CS (1984). Respiratory tract lesions induced by sensory irritants at the RD50 concentration. Toxicol Appl Pharmacol 74(3): 417-29.

CARB (2005b). Annual Statewide Toxics Summary - acrolein Sacramento, CA. http://www.arb.ca.gov/adam/toxics/statepages/acrostate.html.

Cassee FR, Arts JH, Groten JP and Feron VJ (1996a). Sensory irritation to mixtures of formaldehyde, acrolein, and acetaldehyde in rats. Arch Toxicol 70(6): 329-37.

Cassee FR, Groten JP and Feron VJ (1996b). Changes in the nasal epithelium of rats exposed by inhalation to mixtures of formaldehyde, acetaldehyde, and acrolein. Fundam Appl Toxicol 29(2): 208-18.

CCR (2007). California Code of Regulations Section 93001 Hazardous Air Pollutants Identified as Toxic Air Contaminants. Sacramento, CA: California Office of Administrative Law. 8-20-07. http://ccr.oal.ca.gov/linkedslice/default.asp?SP=CCR-1000&Action=Welcome.

Chhibber G and Gilani SH (1986). Acrolein and embryogenesis: an experimental study. Environ Res 39(1): 44-9.

Claussen U, Hellmann W and Pache G (1980). The embryotoxicity of the cyclophosphamide metabolite acrolein in rabbits, tested in vivo by i.v. injection and by the yolk-sac method. Arzneimittelforschung 30(12): 2080-3.

Darley E, Middleton J and Garber M (1960). Plant damage and eye irritation from ozone-hydrocarbon reactions. Agricul Food Chem 8(6): 483-484.

Doty RL, Cometto-Muniz JE, Jalowayski AA, Dalton P, Kendal-Reed M and Hodgson M (2004). Assessment of upper respiratory tract and ocular irritative effects of volatile chemicals in humans. Crit Rev Toxicol 34(2): 85-142.

Feron VJ and Kruysse A (1977). Effects of exposure to acrolein vapor in hamsters simultaneously treated with benzo[a]pyrene or diethylnitrosamine. J Toxicol Environ Health 3(3): 379-94.

Feron VJ, Kruysse A, Til HP and Immel HR (1978). Repeated exposure to acrolein vapour: subacute studies in hamsters, rats and rabbits. Toxicology 9(1-2): 47-57.

Finkelstein EI, Nardini M and van der Vliet A (2001). Inhibition of neutrophil apoptosis by acrolein: a mechanism of tobacco-related lung disease? Am J Physiol Lung Cell Mol Physiol 281(3): L732-9.

Ginsberg GL, Foos BP and Firestone MP (2005). Review and analysis of inhalation dosimetry methods for application to children's risk assessment. J Toxicol Environ Health A 68(8): 573-615.

Gosselin B, Wattel F, Chopin C, Degand P, Fruchart JC, Van der Loo D and Crasquin O (1979). [A case of acute acrolein poisoning]. Nouv Presse Med 8(30): 2469-72.

Grafstrom RC, Sundqvist K, Dypbukt JM and Harris CC (1987). Pathobiological effects of aldehydes in cultured human bronchial cells. IARC Sci Publ(84): 443-5.

Gurtoo HL, Marinello AJ, Struck RF, Paul B and Dahms RP (1981). Studies on the mechanism of denaturation of cytochrome P-450 by cyclophosphamide and its metabolites. J Biol Chem 256(22): 11691-701.

IARC (1995). Dry Cleaning, Some Chlorinated Solvents and Other Industrial Chemicals. IARC monographs 63: 337-371.

Kane LE, Barrow CS and Alarie Y (1979). A short-term test to predict acceptable levels of exposure to airborne sensory irritants. Am Ind Hyg Assoc J 40(3): 207-29.

Kimbell JS, Overton JH, Subramaniam RP, Schlosser PM, Morgan KT, Conolly RB and Miller FJ (2001). Dosimetry modeling of inhaled formaldehyde: Binning nasal flux predictions for quantitative risk assessment. Toxicological Sciences 64(1): 111-121.

Kutzman R. (1981). A subchronic inhalation study of Fischer 344 rats exposed to 0, 0.4, 1.4, or 4.0 ppm acrolein. National Toxicology Program: Interagency Agreeement No. 222-Y01-ES-9-0043. Brookhaven National Laboratory. Upton, NY

Kutzman RS, Popenoe EA, Schmaeler M and Drew RT (1985). Changes in rat lung structure and composition as a result of subchronic exposure to acrolein. Toxicology 34(2): 139-51.

Lam CW, Casanova M and Heck HD (1985). Depletion of nasal mucosal glutathione by acrolein and enhancement of formaldehyde-induced DNA-protein cross-linking by simultaneous exposure to acrolein. Arch Toxicol 58(2): 67-71.

Leikauf GD, Doupnik CA, Leming LM and Wey HE (1989a). Sulfidopeptide leukotrienes mediate acrolein-induced bronchial hyperresponsiveness. J Appl Physiol 66(4): 1838-45.

Leikauf GD, Leming LM, O'Donnell JR and Doupnik CA (1989b). Bronchial responsiveness and inflammation in guinea pigs exposed to acrolein. J Appl Physiol 66(1): 171-8.

Linhart I, Frantik E, Vodickova L, Vosmanska M, Smejkal J and Mitera J (1996). Biotransformation of acrolein in rat: excretion of mercapturic acids after inhalation and intraperitoneal injection. Toxicol Appl Pharmacol 136(1): 155-60.

Lyon JP, Jenkins LJ, Jr., Jones RA, Coon RA and Siegel J (1970). Repeated and continuous exposure of laboratory animals to acrolein. Toxicol Appl Pharmacol 17(3): 726-32.

Mahut B, Delacourt C, de Blic J, Mani TM and Scheinmann P (1993). Bronchiectasis in a child after acrolein inhalation. Chest 104(4): 1286-7.

Mannino DM, Homa DM, Pertowski CA, Ashizawa A, Nixon LL, Johnson CA, Ball LB, Jack E and Kang DS (1998). Surveillance for asthma--United States, 1960-1995. MMWR CDC Surveill Summ 47(1): 1-27.

McNulty M, Heck HD and Csasnova-Schmitz M (1984). Depletion of glutathione in rat respiratory mucosa by inhaled acrolein. Fed Proc 43: 575, abstract 1695.

MDH (2002). Health Risk Values for Air - Subchronic HRVs March 2002. Minnesota Department of Health,. http://www.health.state.mn.us/divs/eh/air/hrvtable.htm#sub.

Morris JB, Symanowicz PT, Olsen JE, Thrall RS, Cloutier MM and Hubbard AK (2003). Immediate sensory nerve-mediated respiratory responses to irritants in healthy and allergic airway-diseased mice. J Appl Physiol 94(4): 1563-71.

Nazaroff WW and Singer BC (2004). Inhalation of hazardous air pollutants from environmental tobacco smoke in US residences. J Expo Anal Environ Epidemiol 14 Suppl 1: S71-7.

NTIS. (1981). Acrolein health effects. Final task 6 report. Contract # 68-03-2928. National Technical Information Service. Arlington (VA)

OEHHA. (2001). *Prioritization of toxic air contaminants - children's health protection act - final report*. Available on-line at: <http://www.oehha.ca.gov/air/toxic_contaminants/SB25finalreport.html>.

Parent RA, Paust DE, Schrimpf MK, Talaat RE, Doane RA, Caravello HE, Lee SJ and Sharp DE (1998). Metabolism and distribution of [2,3-14C]acrolein in Sprague-Dawley rats. II. Identification of urinary and fecal metabolites. Toxicol Sci 43(2): 110-20.

Penn A, Nath R, Pan J, Chen L, Widmer K, Henk W and Chung FL (2001). 1,N(2)-propanodeoxyguanosine adduct formation in aortic DNA following inhalation of acrolein. Environ Health Perspect 109(3): 219-24.

Prentiss A (1937). Chemicals in War. In. McGraw-Hill. New York: 139-140.

Roemer E, Anton HJ and Kindt R (1993). Cell proliferation in the respiratory tract of the rat after acute inhalation of formaldehyde or acrolein. J Appl Toxicol 13(2): 103-7.

Roux E, Hyvelin JM, Savineau JP and Marthan R (1999). Human isolated airway contraction: interaction between air pollutants and passive sensitization. Am J Respir Crit Care Med 160(2): 439-45.

Slott VL and Hales BF (1986). The embryolethality and teratogenicity of acrolein in cultured rat embryos. Teratology 34(2): 155-63.

Takabe W, Niki E, Uchida K, Yamada S, Satoh K and Noguchi N (2001). Oxidative stress promotes the development of transformation: Involvement of a potent mutagenic lipid peroxidation product, acrolein. Carcinogenesis (Oxford) 22(6): 935-941.

U.S.EPA. (2003). Toxicological review of acrolein. EPA/635/R-03/003. U.S. Environmental Protection Agency. Washington DC

Weber-Tschopp A, Fischer T, Gierer R and Grandjean E (1977). [Experimentally induced irritating effects of acrolein on men (author's transl)]. Int Arch Occup Environ Health 40(2): 117-30.

WHO. (1992). *Environmental health criteria 127. Acrolein*. World Health Organization. www.inchem.org/documents/ehc/ehc/ehc127.htm#SectionNumber:10.1.

Yang XM, Wu XL, Choi YE, Kern JC and Kehrer JP (2004). Effect of acrolein and glutathione depleting agents on thioredoxin. Toxicology 204(2-3): 209-218.